

Valaciclovir to prevent vertical transmission of cytomegalovirus after maternal primary infection during pregnancy: a randomised, double-blind, placebo-controlled trial



Keren Shahar-Nissan*, Joseph Pardo*, Orit Peled, Irit Krause, Efraim Bilavsky, Arnon Wiznitzer, Eran Hadar†, Jacob Amiri†

Summary

Background Cytomegalovirus is a common congenital infection, with high morbidity after an early primary maternal infection. No effective means exist to prevent viral transmission to the fetus. We aimed to investigate whether valaciclovir can prevent vertical transmission of cytomegalovirus to the fetus in pregnant women with a primary infection acquired early in pregnancy.

Methods This prospective, randomised, double-blind, placebo-controlled trial was done at the Infectious Feto-Maternal Clinic of Rabin Medical Center (Petach Tikvah, Israel). Pregnant women aged 18 years or older, with serological evidence of a primary cytomegalovirus infection acquired either periconceptionally or during the first trimester of pregnancy, were randomly assigned to oral valaciclovir (8 g per day, twice daily) or placebo from enrolment until amniocentesis at 21 or 22 gestational weeks. Randomisation was done separately for participants infected periconceptionally or during the first trimester and was done in blocks of four. Patients and researchers were masked to participant allocation throughout the entire study period. The primary endpoint was the rate of vertical transmission of cytomegalovirus. Statistical analyses were done according to per-protocol principles. The study was registered at ClinicalTrials.gov, NCT02351102.

Findings Between Nov 15, 2015, and Oct 8, 2018, we enrolled and randomly assigned 100 patients to receive valaciclovir or placebo. Ten patients were excluded, five from each study group; therefore, the final analysis included 45 patients (all singletons) in the valaciclovir group and 45 patients (43 singletons and two sets of twins) in the placebo group. In the valaciclovir group, including both first trimester and periconceptional infections, five (11%) of 45 amniocenteses were positive for cytomegalovirus, compared with 14 (30%) of 47 amniocenteses in the placebo group ($p=0.027$; odds ratio 0.29, 95% CI 0.09–0.90 for vertical cytomegalovirus transmission). Among participants with a primary cytomegalovirus infection during the first trimester, a positive amniocentesis for cytomegalovirus was significantly less likely in the valaciclovir group (two [11%] of 19 amniocenteses) compared with the placebo group (11 [48%] of 23 amniocenteses; $p=0.020$). No clinically significant adverse events were reported.

Interpretation Valaciclovir is effective in reducing the rate of fetal cytomegalovirus infection after maternal primary infection acquired early in pregnancy. Early treatment of pregnant women with primary infection might prevent termination of pregnancies or delivery of infants with congenital cytomegalovirus.

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Introduction

Cytomegalovirus is the most common congenital infection in humans worldwide, leading to considerable morbidity in newborns.^{1,2} The estimated prevalence of congenital cytomegalovirus after maternal infection is 0.7–1% of all livebirths.^{1–3} The rate of vertical transmission is 30–40% after a maternal primary infection acquired early in pregnancy.^{1,4,5} The risk of serious congenital morbidity is greatest after a maternal primary infection occurring periconceptionally or during the first trimester.^{2,5–7} Treatment intended to ameliorate the sequelae of infected fetuses and infants, prenatally and postnatally, can include valaciclovir, ganciclovir, or valganciclovir.^{8,9} However, the

potential morbidity and mortality of congenital cytomegalovirus infection warrants antenatal prevention of vertical transmission. Hyperimmune globulin tested for this purpose did not significantly decrease the rate of vertical transmission.¹⁰

Theoretically, early antiviral therapy should be effective in preventing vertical transmission of cytomegalovirus.¹¹ Antiviral drugs used for postnatal treatment of congenital cytomegalovirus infections are not approved for use in pregnancy. Medications such as aciclovir and valaciclovir are considered safe in pregnancy (classified by the US Food and Drug Administration as category B) and have been commonly used to treat herpes simplex infections.

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*Contributed equally

†Joint senior authors

Department of Pediatrics "C", Schneider Children's Medical Center of Israel, Petach Tikvah, Israel (K Shahar-Nissan MD, O Peled PharmD, I Krause MD, E Bilavsky MD); Helen Schneider Hospital for Women, Rabin Medical Center, Petach Tikvah, Israel (J Pardo MD, Prof A Wiznitzer MD, E Hadar MD, Prof J Amir MD); and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (K Shahar-Nissan, O Peled, I Krause, E Bilavsky, J Pardo, Prof A Wiznitzer, E Hadar, Prof J Amir)

Correspondence to: Dr Keren Shahar-Nissan, Department of Pediatrics "C", Schneider Children's Medical Center of Israel, Petach Tikva 4920235, Israel kerens411@gmail.com

Research in context

Evidence before this study

There is no effective intervention to prevent vertical transmission of cytomegalovirus. Hyperimmune globulin, which has been tested for this indication, did not significantly decrease the rate of vertical transmission. Previous studies of high-dose valaciclovir during pregnancy showed high tolerance with adequate placental transfer, reaching therapeutic concentrations in maternal and fetal blood and in the amniotic fluid. In a small non-randomised clinical trial, valaciclovir significantly reduced fetal viral load and improved the outcome of moderately symptomatic fetuses. We searched PubMed for all published studies concerning prevention of congenital cytomegalovirus between Jan 1, 2000, and Jan 1, 2015, using the search terms "cytomegalovirus", "cytomegalovirus prevention", "congenital cytomegalovirus", "valaciclovir", "cytomegalovirus vaccine", and "hyperimmune globulin". There were no language restrictions on the search. We reviewed all publications regarding primary prevention (cytomegalovirus vaccine, behavioural education, hyperimmune cytomegalovirus globulin) and secondary prevention. For antiviral agents for cytomegalovirus prevention, we reviewed all studies regarding cytomegalovirus prevention after solid organ transplantation,

and all studies related to valaciclovir treatment during pregnancy.

Added value of this study

For the first time to our knowledge, we showed that valaciclovir administered to pregnant women with a primary cytomegalovirus infection is effective in preventing vertical transmission of cytomegalovirus, with a reduction in the vertical transmission rate compared with placebo. This effect was mainly observed for primary maternal cytomegalovirus infections acquired in the first trimester. Periconceptional and first trimester primary cytomegalovirus infection is known to cause most of the severe congenital cytomegalovirus sequelae. Effective means of prevention of vertical transmission during this period have not been previously described to our knowledge.

Implications of all the available evidence

Valaciclovir could be a potential preventive measure for congenital cytomegalovirus, effectively reducing vertical transmission. Our results could affect clinical practice guidelines and antenatal management of early primary cytomegalovirus during pregnancy. Future studies are needed to determine the effect of timing and duration of treatment.

Moreover, high-dose valaciclovir has been proven clinically effective in preventing cytomegalovirus disease in transplant recipients.¹² A French study showed good placental transfer of valaciclovir, showing that the drug is concentrated in the amniotic fluid with no accumulation.¹³ After administration of valaciclovir (8 g per day), therapeutic concentrations were found in maternal and fetal blood, and in amniotic fluid.¹³ Leruez-Ville and colleagues⁹ showed that valaciclovir was well-tolerated with rare adverse events in pregnant women.

We aimed to investigate whether valaciclovir can prevent vertical transmission of cytomegalovirus to the fetus in pregnant women with a primary infection acquired early in pregnancy.

Methods

Study design and participants

This prospective, randomised, double-blind, placebo-controlled trial was done at the Infectious Feto-Maternal Clinic of Rabin Medical Center (Petach Tikvah, Israel).

Pregnant women aged 18 years or older, with serological evidence of a primary cytomegalovirus infection acquired during the periconceptional period (within 4 weeks before the last reported menstrual period and up to 3 weeks of gestation) or the first trimester of pregnancy, were included in the study. Participants were either referred to the clinic because of suspected primary cytomegalovirus infection or by their physician specifically for this study. Serological screening for cytomegalovirus in pregnancy is not mandatory in Israel but is regularly done by most obstetricians either before or during the first trimester of

pregnancy. Women were included before the 16th week of gestation so that a minimum of 6 weeks of treatment could be achieved. All participants consented to undergo amniocentesis and provided written informed consent. Women who were unable to swallow capsules, suffered from severe vomiting or any pre-existing liver disease, renal dysfunction, or bone marrow suppression, received antiviral therapy or immunosuppressive therapy before the study, or had a known hypersensitivity to aciclovir were excluded.

Serological proof of infection was verified according to seroconversion of IgG from negative to positive during pregnancy, or an IgG with low avidity in the presence of specific IgM and a subsequent, substantial rise in IgG titre.^{11,14} Estimation of the time of maternal cytomegalovirus infection was in accordance with Revello and colleagues' definitions.¹⁰ IgG avidity less than 15% implied an onset of infection less than 6 weeks previously. Avidity of less than 35% indicated a primary infection acquired less than 12 weeks earlier.¹⁰ Avidity was assessed using the VIDAS CMV Avidity II (BioMérieux; Marcy-l'Étoile, France). Serological data of study participants are available in the appendix (pp 1–4).

The trial was approved by the ethics committee of Rabin Medical Center.

Randomisation and masking

After signing an informed consent form, participants were randomly assigned to valaciclovir or placebo. Randomisation was done with computer-generated random number tables. Randomisation was done

See Online for appendix

separately for participants infected periconceptionally or during the first trimester, and was done in blocks of four; two of every four participants received drug, and the remaining two received placebo. Each recruited patient received a serial randomisation code. This code matched the randomisation code on the study medication bottle labels. The bottles were identical, and there was no way to know which contained valaciclovir and which placebo.

The physicians of the study group enrolled the participants, with randomisation done by a separate designated pharmaceutical team outside the hospital, who provided participants with a randomisation number in a sequential matter. The designated randomisation code remained blinded throughout study conduct.

Participants in the treatment arm received valaciclovir (8 g per day); participants in the control group received the same number of identical-looking placebo tablets. Both valaciclovir and placebo were prepared by an outside pharmacy and delivered in boxes labelled with only the randomisation number in order to maintain masking. Patients and researchers were masked to participant allocation throughout the entire study period.

Procedures

Valaciclovir was pulverised and dispensed in capsules, each containing 500 mg valaciclovir and 200 mg inactive ingredients. Participants were instructed to ingest eight capsules in the morning and eight in the evening, totalling 8 g per day. Placebo capsules of lactose monohydrate (233 mg), carboxymethyl cellulose (233 mg), and calcium carbonate (233 mg) were administered in identical gelatin capsules and in the same regimen as valaciclovir. Treatment was initiated at the recruiting visit until the day of amniocentesis and was done at least 7 weeks after the estimated time of maternal infection and after the 21st week of gestation. Vertical transmission was detected by PCR of amniotic fluid, which was sent to the Central Virology Laboratory of the Israeli Ministry of Health (Ramat Gan, Israel). Participants who changed their mind and decided not to undergo amniocentesis continued treatment until the estimated time that the amniocentesis would have been done.

Follow-up visits were scheduled every 4 weeks until amniocentesis. At each visit, participants were assessed for adverse events. A complete blood count and full chemistry panel were done to assess drug toxicity. Compliance was assessed by pill counting and a questionnaire. In all cases of cytomegalovirus-positive amniotic fluid on PCR, a follow-up ultrasound was done, including a detailed and targeted fetal anatomy evaluation and neurosonography. Fetal brain MRI was done between 32 weeks and 34 weeks of gestation. Postnatal evaluation in all infants included confirmation of cytomegalovirus infection by urinary PCR.

Outcomes

The primary endpoint was the rate of vertical transmission of cytomegalovirus. If amniocentesis was not done (because of maternal refusal), it was presumed to be negative in a cytomegalovirus-negative infant and positive in a cytomegalovirus-positive infant, since amniocentesis is negative only in 4–8% of cases of positive cytomegalovirus postnatal urinary PCR after an early maternal infection.^{15,16}

Data analysis was done separately with and without participants who declined amniocentesis to assure validity of the results. Postnatal evaluation of infected infants included a full physical examination, blood count, liver function tests, brain ultrasound, hearing assessment by brainstem evoked audiometry, and an ophthalmological examination. Follow-up of neonate growth, development, and hearing status was done in the cytomegalovirus follow-up clinic or by a maternal telephone interview.

Statistical analysis

A sample size of 38 (corrected for continuity from 32) patients for each study group was originally calculated as sufficient to detect an assumed reduction in the incidence of cytomegalovirus transmission from 40% in the placebo group to 10% in the valaciclovir group, with 80% power by two-sided test at a 5% significance level. Statistical analyses were done according to per-protocol principles. We used Fisher's exact test to compare proportions and the independent *t* test to compare means between groups at baseline. Primary analyses included only participants who received at least one dose of study drug. To investigate correlation between twin fetuses in the study we used a generalised linear mixed model to

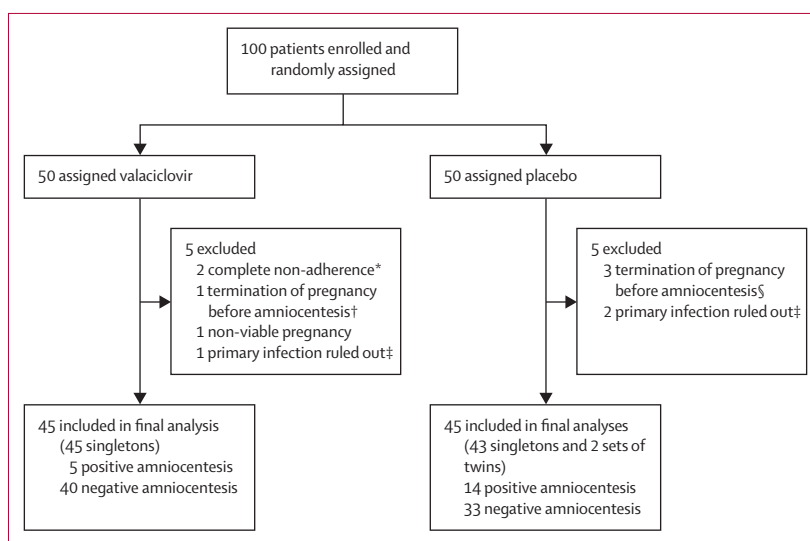


Figure 1: Trial profile

*Refusal to swallow the study drug. †Because of fetal anomalies suggesting a genetic disease (pathological report confirmed trisomy 18). ‡Falsely interpreted cytomegalovirus serology. §Without findings consistent with fetal cytomegalovirus infection.

	Valaciclovir (n=45)	Placebo (n=45)
Fetuses	45	47
Maternal age, years	32.7 (4.1)	31.1 (4.0)
Gestational age at infection, weeks		
–3 to conception	11 (24%)	14 (31%)
1–4	20 (44%)	15 (33%)
5–8	11 (24%)	15 (33%)
9–12	3 (7%)	3 (7%)
Parity		
0	5 (11%)	6 (13%)
1	22 (49%)	23 (51%)
2	9 (20%)	10 (22%)
3	7 (16%)	7 (16%)
≥4	2 (4%)	1 (2%)
Gestational age at treatment initiation, days	80.76 (20.19)	78.21 (16.48)
Twins*	0	4 (9%)
Amniocentesis done*	43 (96%)	42 (90%)
Time from infection to therapy initiation, days	53.51 (19.06)	54.06 (20.16)

Data are n, mean (SD), or n (%). *Denominator is the number of fetuses.

Table 1: Baseline demographic and clinical data of study participants

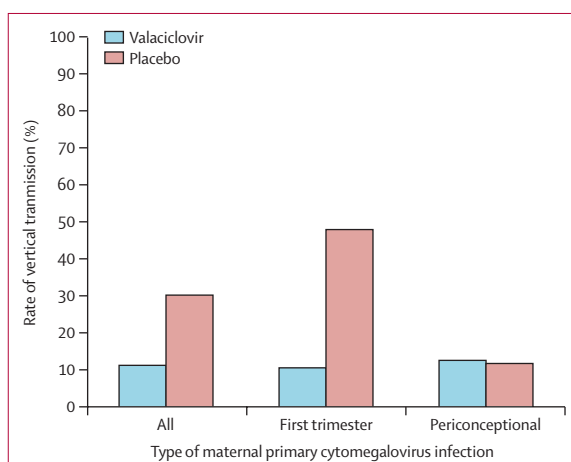


Figure 2: Rate of vertical transmission among study participants

evaluate the outcomes between the two study groups, adjusting for gestational age and period of therapy. $p < 0.05$ was considered the threshold of statistical significance.

Analyses were done with IBM SPSS version 25, R version 3.5.3, and R-studio version 1.1.463. The trial is registered with ClinicalTrials.gov, NCT02351102.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Nov 15, 2015, and Oct 8, 2018, we enrolled and randomly assigned 100 patients (figure 1). Ten patients were excluded, five from each study group. In the three participants excluded from the study after repeat serology ruled out primary infection, initial serology showed positive IgM with negative or borderline IgG, which did not increase in subsequent tests, therefore primary infection was ruled out after recruitment. The final analysis included 45 patients (all singletons) in the valaciclovir group and 45 patients (43 singletons and two sets of twins) in the placebo group. Baseline characteristics were similar between the two study groups (table 1). Median gestational age at initiation of therapy was 76 days (IQR 69–95).

In the valaciclovir group, including both first trimester and periconceptional infections, five (11%) of 45 amniocenteses were positive for cytomegalovirus, compared with 14 (30%) of 47 amniocenteses in the placebo group ($p = 0.027$; odds ratio [OR] 0.29, 95% CI 0.09–0.90 for vertical cytomegalovirus transmission). Among participants with a primary cytomegalovirus infection during the first trimester, a positive amniocentesis for cytomegalovirus was significantly less likely in the valaciclovir group (two [11%] of 19 amniocenteses) compared with the placebo group (11 [48%] of 23 amniocenteses; $p = 0.020$; figure 2). No significant difference in the rate of positive amniocentesis was observed between the study groups among participants with a primary cytomegalovirus infection acquired periconceptionally (three [12%] of 26 amniocenteses in the valaciclovir group vs three [13%] of 24 amniocenteses in the placebo group; $p = 0.91$; figure 2).

Although all patients agreed to undergo amniocentesis upon recruitment, six participants (one with a twin gestation, therefore seven fetuses) were recruited but refused amniocentesis. Negative urine cytomegalovirus PCR was observed in three (43%) of seven neonates; therefore, amniocentesis was presumed to be negative for the purpose of our data analysis. Amniocentesis results for the four neonates with positive urine PCR were presumed positive for the purpose of our data analysis (three of the neonates—twins and another fetus—were in the placebo group and one in the valaciclovir group). In a post-hoc analysis, after exclusion of these six participants (and seven fetuses), the primary endpoint results remained unchanged, with four (9%) of 43 amniocenteses positive in the valaciclovir group compared with 11 (26%) of 42 in the placebo group ($p = 0.038$).

Patients with a primary cytomegalovirus infection acquired during the first trimester began treatment significantly earlier (and closer to the maternal infection) compared with patients with a periconceptional infection (table 2). Mothers presenting with a cytomegalovirus-positive amniocentesis in the valaciclovir group began treatment significantly later compared with mothers presenting with a cytomegalovirus-negative amniocentesis (table 3).

	Placebo			Valaciclovir			Total		
	First trimester (n=23)	Periconceptual (n=24)	p value	First trimester (n=19)	Periconceptual (n=26)	p value	First trimester (n=42)	Periconceptual (n=50)	p value
Time, days	41·09 (12·89)	66·50 (18·00)	<0·0001	43·84 (14·16)	60·58 (19·29)	0·0026	42·33 (13·38)	63·42 (18·73)	<0·0001

Data are mean (SD), unless otherwise indicated.

Table 2: Time from maternal infection to treatment initiation, by timing of maternal infection

	Placebo				Valaciclovir			
	Negative (n=33)	Positive (n=14)	Total (n=47)	p value	Negative (n=40)	Positive (n=5)	Total (n=45)	p value
Time, days	58·76 (21·36)	43 (11·27)	54·06 (20·16)	0·013	50·75 (17·63)	75·60 (16·71)	53·51 (19·06)	0·0047

Data are mean (SD), unless otherwise indicated.

Table 3: Time from maternal infection to treatment initiation, by amniocentesis result

Low adherence rates (<80%) were noted in six patients in the placebo group and three in the valaciclovir group. Suboptimal adherence rates (80–89%) were observed in three patients in the placebo group and two in the valaciclovir group. The rate of adverse events did not differ significantly between the two study groups ($p=0\cdot49$). Adverse events in the valaciclovir and placebo group, respectively, were thrombocytopenia (one [2%] of 45 participants *vs* zero of 45 participants, with a minimum platelet count of 104 000 per μL that increased spontaneously without changing the dose), nausea (13 [29%] of 45 participants *vs* ten [22%] of 45 participants), headache (nine [20%] of 45 participants *vs* six [13%] of 45 participants), abdominal pain (four [9%] of 45 participants *vs* two [4%] of 45 participants), and non-specific rash (one [2%] of 45 participants *vs* three [7%] of 45 participants). Some participants had more than one adverse event. None of these adverse events were clinically significant nor caused functional impairment; hence, no dose adjustments or treatment cessations were required.

In the valaciclovir group, 43 fetuses were carried to term, one pregnancy was terminated at a late stage due to cytomegalovirus-related fetal damage observed on fetal brain ultrasound and MRI, and one pregnancy was terminated at a late stage due to MRI findings consistent with a familial genetic disorder unrelated to cytomegalovirus infection. In the placebo group, 41 fetuses were carried to term, two pregnancies were terminated because of radiological evidence of cytomegalovirus-related fetal damage, one pregnancy was terminated at 31 weeks because of evidence of posterior urethral valves (without any evidence of cytomegalovirus-related damage), and three pregnancies were terminated on maternal request, after the results of a positive amniocentesis (without any evidence of cytomegalovirus-related damage). When calculating infant outcomes, we excluded pregnancies terminated for reasons unrelated to cytomegalovirus. Overall, the evidence of fetal cytomegalovirus-related symptomatic infection (during pregnancy or after birth) was observed in three (7%) of

44 fetuses and infants in the valaciclovir group versus seven (16%) of 43 fetuses and infants in the placebo group. Postnatal evidence of cytomegalovirus morbidity comprised unilateral or bilateral sensorineural hearing loss (six infants) or postnatal sonographic findings on head ultrasound (focal bilateral subependymal cysts in one infant). In the placebo group, five infants had hearing loss. In the valaciclovir group, one infant had hearing loss and one had subependymal cysts without any other manifestations. Overall, participants in the valaciclovir group had a lower odds of any cytomegalovirus-related morbidity compared with the placebo group (OR 0·38, 95% CI 0·09–1·56). Six infants were cytomegalovirus-positive at birth despite a negative amniocentesis, two in the placebo group, and four in the valaciclovir group. One infant in the treatment group was asymptomatic with bilateral subependymal cysts observed on brain ultrasound, and the remaining five were asymptomatic.

Discussion

In this randomised, double-blind, placebo-controlled trial of prevention of vertical transmission of cytomegalovirus after primary maternal infection, treatment with valaciclovir reduced the rate of vertical transmission. Compliance rates were high and the drug was well tolerated.

To our knowledge, our study is the first to investigate antiviral treatment for prevention of maternal–fetal cytomegalovirus transmission after primary maternal infection. We showed a reduction in the fetal infection rate in the valaciclovir group compared with the placebo group. Although congenital cytomegalovirus infection causes substantial morbidity in neonates and seriously affects their health in adulthood, there is no preventive treatment for transmission of infection. The only therapy previously studied for this purpose in a randomised, placebo-controlled trial¹⁰ was hyperimmune globulin, which showed no significant reduction of fetal infection.

The results of our study show the efficacy of preventive treatment for viral transmission after maternal cytomegalovirus infection. Treatment was shown to be most effective when started as soon as possible after presumed maternal infection. The reduction of fetal transmission was most significant in mothers who were infected during the first trimester, as treatment was initiated earlier, and closer to the onset of the maternal infection. Furthermore, the five fetuses infected in the valaciclovir group began therapy significantly later than those who were uninfected. The sequence of events leading to fetal infection is most probably maternal viraemia, placental infection, and fetal haematogenous dissemination.¹⁷ This sequence of events takes around 7 weeks. In the five infected fetuses in the valaciclovir group, treatment was initiated a mean of 75 days after maternal infection, well after the timeframe for fetal infection. These data imply that early detection of primary cytomegalovirus infection is crucial for successful prevention of transmission by valaciclovir, which will require a major change in diagnostic policy (ie, early generalised screening of women who are seronegative). In 2014, Revello and colleagues¹⁰ reported that the unavailability of a therapeutic intervention of proven efficacy in the case of documented maternal infection was a major obstacle to implementation of routine serological screening of pregnant women. In light of this study, we believe that it might be time to reconsider.

In the subgroup of women who had primary cytomegalovirus infection in the periconceptional period, treatment did not significantly modify the rate of vertical transmission, possibly because of late initiation of treatment after maternal primary infection. Treatment was initiated after a mean of 60·58 days in the periconceptional group compared with 43·84 days in the first trimester group. Therefore, by the time mothers discovered a primary infection, the fetus might have already been infected, as diagnosis of primary cytomegalovirus infection is usually made during the first trimester of pregnancy (the first prenatal visit takes place around week 6–7 of pregnancy). Treatment initiated at the time of diagnosis was further from the time of primary infection in the periconceptional group. In an open-label phase 2 study,⁹ the authors observed that valaciclovir treatment of symptomatic congenital cytomegalovirus infections significantly reduced fetal viral load and improved the outcome of moderately symptomatic fetuses. Our study expanded on this finding and showed that valaciclovir is safe and effective in preventing vertical transmission. If treatment of symptomatic fetuses with valaciclovir improved clinical outcomes, it can be assumed that treating infected fetuses in utero, before the onset of symptoms, might also improve clinical outcomes. However, our study was underpowered to show a significant difference in neonatal outcomes. The only patient in the valaciclovir group who terminated her pregnancy because of sonographic signs of fetal brain damage,

commenced treatment 15 weeks after a presumed primary infection and in her 15th week of pregnancy.

Our valaciclovir dose regimen required 16 tablets a day, which was difficult to comply with. However, treatment compliance was good and there were few adverse events. We hope that in the future a smaller number of daily tablets for the same dose will be available.

The main limitation of our study was the small sample size, which was designed to encompass the minimum number of patients needed for statistical power because of anticipated difficulties in recruitment of pregnant women to a placebo-controlled trial. Another limitation was the calculation of the timing of the maternal infection, which was based only on serological assays; however, this method was used in both study groups, so bias was unlikely. An additional limitation of this study was the use of per-protocol analysis. Although this does not compromise the efficacy that we report in this study, this may mean that study drug is less effective outside the study setting. Another limitation of the study was the issue of positive cytomegalovirus PCR in neonates after negative amniocentesis. There were six such newborns, four in the treatment group and two in the placebo group. Among these infants, there was a possibility of late fetal infection during the late second or third trimester, after amniocentesis. Antiviral treatment was intended to suppress the virus during the first trimester, which is the most dangerous time for fetal damage. Delayed fetal infection after cessation of treatment is expected in some patients because of the increased viral load. Furthermore, the rate of transmission increases with advancing gestational age,⁷ and therefore these infants were probably infected late in pregnancy and would have had a much better prognosis than those infected during early stages of pregnancy.¹⁸

In conclusion, we showed, for the first time to our knowledge, evidence for efficacy of valaciclovir in prevention of vertical transmission of cytomegalovirus after first trimester primary maternal infection. Adoption of this strategy could reduce the rate of symptomatic congenital cytomegalovirus in neonates. Combined with appropriate screening and further strengthening in larger trials, this strategy might safely and effectively alleviate neonatal short and long-term cytomegalovirus-related morbidity.

Contributors

KS-N, JP, and JA conceived and designed the study. KS-N, JP, OP, EH, and JA acquired the data. KS-N, JP, OP, IK, EB, AW, EH, and JA analysed and interpreted the data. All authors drafted or revised the manuscript, provided final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Declaration of interests

We declare no competing interests.

Data sharing

The study dataset, including anonymised individual participant data and a data dictionary defining each field in the dataset, will be available to appropriate academic parties for qualified researchers upon request

from the principal investigator, KS-N. Data availability is in accordance with the hospital ethics committee approval, and subject to submission of a suitable and clinically important study protocol, provided with a signed data access agreement. Other related documents, the study protocol, and informed consent form will be made available if necessary for the proposed study. All data will be made available upon publication of this manuscript and be shared via email.

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